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| 09/885,287 | 06/21/2001 | Andreas Sewing | MERCK-2261 | 2670 |

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| EXAMINER | |
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| GOLLAMUDI, SHARMILA S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1616 | |

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/885,287 | SEWING ET AL. | |
| | Examiner | Art Unit | |
| | Sharmila S. Gollamudi | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,10-19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Receipt of Request for Continued Examination and Amendments/Remarks filed January 6, 2006 is acknowledged. Claims **1-8, 10-19, 21, and 23-27** are pending in this application.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1/6/06 has been entered.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 1-8, 10-19, 21, and 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

Claim 1 has been amended to recite "wherein the mineralized collagen matrix is constructed in the form of layers, and each layer comprises a network of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite." This does not

have support in the specification. Applicant cites page 5, lines 12-19, 30-31 for support. Although, lines 30-35 of page 5 provide support for the collagen matrix to have layers, this does not provide support for each layer specifically having the combination of amorphous calcium phosphate clusters, collagen, and crystalline hydroxyapatite. Applicant cites page 9, lines 16-21 and page 11, lines 4-14 to provide support. The examiner does not find any support on page 9 and on page 11, the examiner notes the combination of hydroxyapatite and collagen; however this does not provide support for the *specific* combination of amorphous calcium phosphate clusters, collagen, and crystalline hydroxyapatite and I more than one layer. Applicant cites page 12, lines 6-8 for support. The examiner notes the combination of collagen, amorphous calcium phosphate, and crystalline hydroxyapatite; however the examiner does not find support for multiple layers comprising this combination or amorphous calcium *clusters*. The examiner notes on page 10, the applicant has one layer comprising collagen and spherical calcium phosphate clusters. However, this does not provides support for amorphous calcium phosphate clusters or the specific combination of collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 2-3 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 1 has been amended to recite "wherein the mineralized collagen matrix is constructed in the form of layers, and each layer comprises a network of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite."

Claim 2 fails to further limit the parent claim since claim 1 already recites that the collagen matrix is in the form of layers.

Claim 3 recites "wherein the calcium phosphate phase of the matrix contains amorphous calcium phosphate, hydroxyapatite, octacalcium phosphate, brushite or mixtures thereof. Claim 3 depends on claim 1 which requires amorphous calcium phosphate and hydroxyapatite; thus the claim is vague and indefinite. If applicant intends to claim the collagen matrix further comprises octacalcium phosphate or brushite, the examiner suggests amending the claim accordingly to clarify the claim limitation.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1-4, 10-16, 18-19, 21, 23, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315).**

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The calcium phosphate is selected from either tricalcium phosphate and hydroxyapatite is taught. See claims and examples. The particle range of the calcium phosphate is 2-5 microns. See example 2. The micropores in the calcium phosphate compound coating also encourages better adhesion of collagen. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not teach the combination of amorphous calcium phosphate and hydroxyapatite.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate

minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Shirkanzadeh and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen.

Note that the process limitations in claims 11-19 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the

product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to layers, collagen in combination with mineral components implicitly tends to separate phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's argument.

***Response to Arguments***

Applicant argues that that "applicant's meaning of mineralize" is different and pertains to the field of bio-mineralization. Applicant argues that an inventor may be his or her own lexicographer. Applicant argues that Shirkanzadeh teaches a calcium phosphate layer that encourages adhesion of macromolecules such as collagen. Applicant argues this structure is too large to promote mineralization since Shirkanzadeh's crystal sizes are too large to promote mineralization. Applicant submits Figure 1, which shows the structure of Shirkanzadeh and submits Figure 3 as the instant invention wherein the crystal sizes are less than 1 micron.

Applicant's arguments filed 1/6/06 have been fully considered but they are not persuasive. The examiner notes that the applicant may be his or her own lexicographer however applicant has neither defined the term in the specification explicitly nor has the applicant pointed out where in the specification the term is defined. The examiners points to MPEP 2106 where it states "Any special meaning assigned to a term must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." The applicant has not pointed to the page or pages in which the specification implicitly provides a definition of the term. Furthermore, the term "bone analogous coating" is

also not defined. Therefore, the examiner is permitted the broadest reasonable interpretation. Mineralize is defined by Merriam-Webster's Collegiate Dictionary as: "to impregnate or supply with mineral". Lastly, the examiner points out that both the prior art and the instant invention are in the same field of endeavor and thus applicant's argument that the instant invention is in the field of bio-mineralization is unclear.

It is noted that in the arguments of 12/21/04, applicant argued that the difference between the instant structure and Shirkanzadeh is the process of making the composition wherein the instant invention is "not just a simple mixture of calcium phosphate and collage". However, independent claim 1 does not recite any process steps, which provide this "unique structure". Although applicant argues that the particle size is critical for mineralization, applicant does not claim the calcium phosphate particle size in independent claim 1. Further, the applicant submitted a Figure on 12/21/04 that purportedly is a figure of the implant structure in US '921. However, the Figure is that of the implant disclosed by Shirkanzadeh in Materials Letters, volume 14. The applicant has not submitted the article for the examiner to determine if the Figure is indeed similar to that disclosed in US '941 and if the coating is prepared under similar conditions as described in US '941.

**Claims 5, 7-8, 17, and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Kwan et al (5776193).**

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50

microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns. See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not specify the type of collagen utilized, the diameter of the calcium phosphate crystals, or drugs.

Kwan et al teach a mineralized Type I collagen matrix containing calcium phosphate for bone grafting. Kwan teaches the suitability of collagen or collagen derivatives for the matrix, with a preference for Type I. The matrix may contain other agents such as growth factors, calcitonin, and binders such as gelatin. See column 3, lines 56-65 and column 4, lines5-10. By utilizing drugs such as growth factors in the matrix, the matrix may also provide a substrate to which the host's growth factors may bind and facilitate repair. See column 5, lines 46-60. Kwan teaches that the particles are of an average diameter of less than five microns since these particles are small enough to phagocytized to stimulated local reaction and further bone resorption. See column 5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Shirkanzadeh et al and Kwan et al since both teach collagen matrix containing calcium phosphate. One would be motivated to look to the guidance of Kwan

et al and utilize instant collagen type since the instant collagen type is recognized as suitable material for implants.

Further, one would be motivated to utilize instant active agents such as growth factors to facilitate repair. Therefore, the selection of the pharmaceutical contained in the implant depends on the intended use of the implant and the treatment plan.

Lastly, it is deemed obvious to one of ordinary skill in the art at the time the invention was made to manipulate the parameters of particle size of the calcium phosphate thorough routine experimentation, absent evidence to the contrary. Additionally, one would be motivated to utilize the instant diameter range since Kwan teaches the utilization of particles with less than 5 microns to further bone resorption.

**Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Sauk et al (4,780,450).**

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns.

See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh et al and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

**Claims 1-3, 5-8, 10-19, 23, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee et al (5,543,441).**

Rhee et al teach solid implants coated with collagen-polymer conjugates, which may contain particulates such as calcium phosphate. The dried collagen-PEG composition has sponge-like properties and when incorporated with growth factors, serve as an effective controlled-release device. See column 7, lines 1-6. Collagen Type I, II, and III are taught. See

column 8. Example 7 teaches a prior art coating composition contain collagen (Type I) and hydroxyapatite and tricalcium phosphate and the inventive coating composition comprising collegen-PEG and hydroxyapatite and tricalcium phosphate. Rhee teaches the collagen and HA/TCP separate into phases. Rhee teaches the additional use of gelatin beads. Rhee teaches the collagen-polymer and HA+TCP (hydroxyapatite and tricalcium phosphate) exhibits high tensile strength. Example 5 discloses coating a titanium implant with the coating composition of the inventive collagen- polymer conjugate, however calcium phosphate is not used in coating composition of this example.

Although Rhee teaches the instant coating composition, example 7's coating composition is not specifically utilized to coat a metal implant.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Rhee et al and utilize the coating composition of example 7 to coat the metallic implant of example 5. One would have been motivated to do so since although Rhee does not exemplify this embodiment, Rhee clearly suggests the use of the inventive collagen-polymer conjugate with particulates such as HA and TCP for coating implants. Therefore, the instant invention is prima facie obvious in view of the general disclosure of Rhee et al.

Note that the recitation "wherein the coating is obtained by precipitating phosphate from a solution in the presence of collagen" and process limitation in claims 11-19 and 27 are product-by-process limitation. According to MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product

in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, collagen in combination with mineral components implicitly tends to separate phases or layers. Note column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

With regard to claim 6, Rhee teaches the use of collagen type I, II, and III and it is prima facie obvious to utilize a mixture since Rhee teaches all forms of collagen may be used.

***Response to Arguments***

Applicant argues that Rhee teaches an implant coated with a collagen-polymer conjugate, which may be combined with calcium phosphate and not a collagen matrix mineralized with calcium phosphate. Applicant argues that there is nothing in Rhee that teaches a network of collagen interconnected with calcium phosphate. Lastly applicant argues that "applicant's meaning of mineralize" is different and pertains to the field of bio-mineralization. Applicant argues that an inventor may be his or her own lexicographer.

Applicant's arguments filed 1/6/06 have been fully considered but they are not persuasive. Firstly, the examiner points out that the claims recite open claim language, i.e. comprising and thus the scope of the claims does not exclude the use of the polymer conjugate.

Secondly the examiner notes that the applicant may be his or her own lexicographer however applicant has neither defined the term in the specification explicitly nor has the applicant pointed out where in the specification the term is defined. The examiners points to MPEP 2106 where it states "Any special meaning assigned to a term must be sufficiently clear in

the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." The applicant has not pointed to the page or pages in which the specification implicitly provides a definition of the term. Furthermore, the term "bone analogous coating" is also not defined. Therefore, the examiner is permitted the broadest reasonable interpretation. Mineralize is defined by Merriam-Webster's Collegiate Dictionary as: "to impregnate or supply with mineral". Lastly, the examiner points out that both the prior art and the instant invention are in the same field of endeavor and thus applicant's argument that the instant invention is in the field of bio-mineralization is unclear.

Assuming arguendo that Rhee polymer conjugate prevents the formation of the network, the examiner points out example 7 wherein Rhee teaches a prior art coating formulation that comprises instantly claimed collagen, HA, and calcium phosphate This coating composition has the same components as instantly claimed and separates into phases and thus must have the same properties as the instantly claimed coating since similar chemical compositions cannot have mutually exclusive properties. See MPEP 2112.01 II.

If applicant is contending that the process limitations yield a different structure and different coating, then the examiner suggests proving evidence since it is the applicant's burden to prove the difference. See MPEP 2113. It is noted however that the independent claim does not have any product-by-process limitations.

**Claims 1-5, 8, 10-16, 18-19, 21, 23, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315).**

Worch et al disclose a metallic substrate (titanium) having a polyphase oxide coating. The polyphase oxide coating is produced by bringing the metallic substrate into contact with an

organic and/or inorganic component to be integrated into the polyphase oxide coating such that the inorganic and/or organic phases are present at or in the direct vicinity of the substrate surface and by simultaneously or subsequently anodically polarizing the substrate material in an electrolytic solution. See abstract. The process of coating the implant yields a two-layer oxide coating, where the outer layer is the inorganic and/or the organic phase. See column 2, lines 32-45. The inorganic component is calcium phosphate and the organic component is Type I collagen. See column 2, lines 46-60. Claim 1 envisages a combination of an organic phase and inorganic phase and claim 4 envisages calcium phosphate as the inorganic phase. Example 1 discloses a coating thickness of 250 nm (.250 micrometers) on the metallic implant. Worch discloses a process wherein the metallic implant is immersed in a collagen solution at the instant pH and temperature and then coated again with a phosphate solution. Note that the use of calcium ions in this solution is clearly envisaged as noted in column 2, lines 46-60 and claim 4.

Although Worch teaches the use of calcium phosphates as the inorganic phase, Worch does not teach specify the form of calcium phosphate. Also Worch does not teach the incorporation of components as recited in claim 4 (doping agents) or 8 (medicaments).

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to

collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Worch and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phases and collagen wherein it is clear that Worch contemplates utilizing more than one form of calcium phosphate. Further, on column 1, lines 45-55, Worch states the deficiency of the prior art is that it only utilizes resorbable calcium phosphate and not hydroxyapatite and thus "the complete character of the implant is lost". Thus, one would have expected success with the instant combination.

With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or

carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite.

With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Note that the process limitation in claims 11-19 and 27 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, it is the examiner's position that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

***Response to Arguments***

Applicant argues that the claims have been amended to recite the coating is "adhered to the metallic implant which overcomes the rejection over Worch et al. Applicant argues that the coating of Worch are embedded in the oxide surface of the implant and not deposited on the implant surface. Applicant argues that Worch describes an electrochemical coating process, which forms a two-layered system, wherein the outer layer comprises an organic and/or inorganic phase. Applicant argues that Worch does not describe the process for producing a mineralized collagen matrix.

Applicant's arguments filed 2/25/05 have been fully considered but they are not persuasive. The definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick. The examiner points out that term "adhered to" does not exclude embedding since embedding is a way of joining (sticking) two surfaces together. Worch discloses the phases are integrated by adsorption, sedimentation application, or deposition. See column 2, line 65 to column 3, line 5. Worch also discloses that the inorganic and organic phases are integrated into the oxide phase and extend beyond it. See claim 23. Additionally, Worch discloses the metallic implant is inserted into a collagen solution so that the collagen fibrillae adsorb to the surface of the implant. The examiner notes that the instant examples of the specification also immerse the implant into the collagen solution at the same pH and temperature. Moreover, the examiner notes on page 7 of the instant disclosure, applicant states that the coating the metallic implant may be done via the process disclosed in WO 98/17844. The examiner points out that US '718 is the English equivalent of WO 98/17844. Thus, the prior art and the instant invention must be "adhered" to the metallic implant in the same way. Lastly, although Worch polishes the metallic substrate with oxide (which integrates with the organic and inorganic phases), it should be noted that the claims do not exclude the oxide layer.

**Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Sauk et al (4,780,450).**

The teachings of Worch and Liu have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III

collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

**Claims 7, 17, 24-25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Kwan et al (5776193).**

The teachings of Worch and Liu have been set forth above.

The references does not specify the diameter of the calcium phosphate crystals or the use of gelatin.

Kwan et al teach a mineralized Type I collagen matrix containing calcium phosphate for bone grafting. Kwan teaches the suitability of collagen or collagen derivatives for the matrix, with a preference for Type I. The matrix may contain other agents such as growth factors, calcitonin, and binders such as gelatin. See column 3, lines 56-65 and column 4, lines5-10. By utilizing drugs such as growth factors in the matrix, the matrix may also provide a substrate to which the host's growth factors may bind and facilitate repair. See column 5, lines 46-60. Kwan teaches that the particles are of an average diameter of less than five microns since these particles

are small enough to phagocytized to stimulated local reaction and further bone resorption. See column 5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Worch, Liu, and Kwan et al and utilize the instantly claimed diameter range since Kwan teaches the utilization of particles with less than 5 microns to further bone resorption. Further, a skilled artisan would have been further motivated to add gelatin to the collagen coating since Kwan teaches it acts as a binder.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 1-5, 8, 10-16, 18-19, 21, 23, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 in view of in view of Liu (6,300,315).**

Claim 1 is directed to a coated metallic implant comprising a metallic implant and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to said implant surface, wherein the mineralized collagen matrix is constructed in the form of layers and each layer comprises a network of mineralized collagen fibrils, amorphous calcium phosphate clusters, and crystalline hydroxyapatite.

US patent is directed to a metallic object and a thin polyphase oxide coating, where said polyphase oxide coating is comprised of a first phase, wherein said first phase is a metal oxide phase, and a second phase, wherein said second phase is either an organic phase, an inorganic phase, or a combination of organic and inorganic phases, said polyphase oxide coating is produced by bringing the metallic substrate into contact with either an organic component, an inorganic component, or a combination of organic and inorganic components to be integrated into said polyphase oxide coating such that said second phase is present at or adjacent to the substrate surface and by simultaneously or subsequently anodically polarizing said substrate material in an electrolytic solution, wherein said metallic substrate is selected from the group consisting of aluminum, titanium, tantalum, zirconium, niobium, or their alloys, inclusive of intermetallic phases. Dependent claims are directed to the organic phases comprising collagen and the inorganic phases comprising calcium phosphate phases.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate

minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

The difference between instant claims and US patent's claims is that the independent claim 1 requires specific calcium phosphates, i.e. hydroxyapatite and amorphous calcium phosphate. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the instantly claimed calcium phosphates and arrive at the instantly claimed invention. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phases and collagen wherein it is clear that Worch envisages utilizing more than one form of calcium phosphate in claim 4. Thus, the

instantly claimed calcium phosphate types are considered an obvious modification. Note that the instant claims have comprising language and thus do not exclude the oxide coating. Note the instant claims are rejected over the process claims of US patent since one would necessarily have the coated metallic implant of the instant invention by the process of making and a restriction was not made in US '718.

With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite.

With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Note that the process limitation in claims 11-19 and 27 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, it is the examiner's position that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

***Conclusion***

All the claims are rejected at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616